‘‘ Challenges & innovation trends in Biologics pharmaceutical Formulation’’

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Abstract

Biopharmaceuticals, derived from biological sources, have revolutionized disease prevention and treatment. This comprehensive review explores the concept, definition, and classification of biopharmaceuticals, encompassing recombinant proteins, monoclonal antibodies, vaccines, and nucleic acids. The paper discusses various applications, including therapy, prevention, and diagnosis, highlighting their role in managing cancer, autoimmune diseases, and infectious disorders. Technological advances in formulation development, such as 3D printing and nanotechnology, are examined. Challenges in stability and regulatory frameworks are addressed. Future trends, including process analytical technology and continuous manufacturing, are discussed. This review provides a thorough understanding of biopharmaceuticals, their development, and their impact on modern medicine. The review also explores economic and social implications, highlighting potential cost savings. Collaboration between industry, academia, and regulatory agencies is emphasized to advance the field, facilitating further research and development in biopharmaceuticals. Overall, this review aims to provide a holistic understanding of biopharmaceuticals and their transformative potential in healthcare. Additionally, the review highlights the importance of personalized medicine and the role of biopharmaceuticals in tailoring treatments to individual patients' needs. Furthermore, the review discusses the potential of biopharmaceuticals in addressing emerging global health challenges, such as pandemics and antimicrobial resistance.

Keywords: biopharmaceuticals, recombinant proteins, monoclonal antibodies, vaccines, nucleic acids, disease prevention, therapy, diagnosis.

Introduction

Definition of biopharmaceuticals

The concept of biological medicines emerged in the early 1980s with the introduction of genetically engineered insulin, a groundbreaking therapeutic agent for managing diabetes. In the US and European, a consensus definition has emerged, describing biological medicines as drugs manufactured through advanced biotechnological methods that utilize living cells or their biological building blocks. This broad category spans a diverse array of products, including genetically engineered proteins, targeted antibodies, preventive vaccines, plasma-derived therapies, cell-based treatments, tissue-derived products from human or animal sources, and genetic materials.(1)

Biological therapies, also known as biotherapeutics or biologics, are medicinal products derived from living organisms or their components. These complex products are composed of biomolecules, peptides, genetic material, living cells, or tissues, and are typically produced through biological extraction or synthesis from natural sources such as humans, creatures, or microorganisms. Biological therapies, also known as biotherapeutics or biologics, are medicinal products derived from living organisms or their components.

Unlike conventional medicines, which are synthesized through chemical methods, biological therapies are obtained through biological processes. This includes extraction from living organisms or production using genetic engineering technologies. Genetically engineered organisms, such as plants, animals, and microorganisms, also hold great promise for biotherapeutic production. Today, biological therapies play a vital role in modern medicine, with applications including preventive treatments, blood and blood components, immunological products, antigens, hormones, signaling molecules, enzymes, allergenic extracts, cellular therapies, genetic therapies, tissue-based products, targeted antibodies, and genetically engineered products.

Biopharmaceuticals refer to intricate molecules derived from biological sources that are utilized to enhance the health of humans or animals through preventive or therapeutic measures. This category comprises a broad spectrum of biotherapeutic products, including preventive treatments, immunological agents, regulatory peptides, hemostatic agents, biological catalysts, growth promoters, and signaling molecules. The designation "biological medicines"

specifically refers to pharmaceuticals that are distinct from the wider classification of biological products, as they are manufactured through advanced biotechnological methods utilizing genetically engineered cells as production systems. The primary production systems for biological medicines include mammalian cell lines, microbial cells, insect cell cultures, and fungal organisms.(2)

Application

Biopharmaceuticals have a diverse range of clinical uses and offer several benefits for the treatment, anticipation, and conclusion of different infections

Therapy

The primary categories of therapeutic biotherapeutics comprise protein replacement therapy, immunological therapy, cellular therapy, and genetic therapy. These biotherapeutic agents possess the capability to safely and effectively cure or manage diseases by exhibiting physiological activity and executing specific biological functions that target the underlying disease pathology. Biopharmaceuticals, in contrast to traditional chemical drugs, exhibit greater complexity in their production processes, offer various administration routes, and possess distinct pharmacokinetic profiles. The benefits of biopharmaceuticals include enhanced selectivity and reduced nonspecific toxicity; however, they also present challenges such as elevated costs and the potential for antidrug antibody formation, which can diminish efficacy or compromise biosafety. Optimizing treatment can be achieved by refining dosing schedules and employing multiple routes of administration. Furthermore, the financial burden may be alleviated through the utilization of biosimilars.

Prevention

A vaccine represents a crucial biopharmaceutical for the prevention of infectious diseases. Typically, it comprises a biological component that mimics a pathogen, which may be derived from inactivated microorganisms, live attenuated microorganisms, toxoids, or specific surface antigens. Immunization efforts have led to a dramatic decline in the prevalence of various contagious illnesses, including measles, tetanus, and poliomyelitis, with some diseases, such as variola, being totally eliminated. Conversely, there has been a significant surge in the incidence of non-transmissible diseases, including malignancies, cardiovascular ailments, metabolic syndromes, and neurodegenerative disorders. Currently, certain immunizations have been successfully employed to prevent specific types of malignancies; for instance, the human papillomavirus (HPV) immunization has received approval for the prevention of cervical malignancy.

Diagnosis

Biopharmaceuticals hold considerable clinical importance not only in therapy and prevention but also in disease diagnosis. For instance, monoclonal antibodies have proven effective in diagnosing certain cancers and infectious

diseases, with ongoing development of additional applications. Monoclonal antibodies, once generated for a specific substance, can be employed to identify the presence of that substance. Additionally, they play a significant role in immunohistochemistry, which is utilized to detect antigens in fixed tissue sections, as well as in immunofluorescence assays that identify specific proteins or biomarkers solidified tissue areas or inside alive cells. .(3). Biopharmaceuticals are linked to groundbreaking therapies for various diseases, such as cardiovascular conditions, cancer, arthritis, infections and multiple sclerosis.(4)

Types of Biopharmaceutical Formulation

Monoclonal antibodies

In the past twenty years, targeted biologic therapies (mAbs) have revolutionized disease treatment. mAbs have become a preferred treatment option in multiple fields, including cancer treatment, blood disorder management, and immune system disease treatment. The primary monoclonal antibody endorsed for helpful utilize was Orthoclone OKT3 on 1986. This laboratory-developed antibody targets CD3 and was approved for managing kidney transplant rejection..(5).

Monoclonal antibodies (mAbs) were initially produced as murine proteins, which rendered them immunogenic in humans and consequently inappropriate for prolonged therapeutic use. To address this limitation, more humanized mAbs with reduced immunogenicity were engineered through advancements in molecular biology and protein engineering. Various forms of mAbs and traps are currently employed in clinical research.(6).

Mabs are a course of immune globulins, or their fragments, designed to target specific antigens. Derived from a single cell clone, these proteins comprise four interconnected protein chains. The chain feature constant and variable domains, with the variable domains containing three (complementary determining regions) CDRs that manage the antibody's official specificity.

The antibody's quaternary structure consists of three main segments: two (antigen-binding fragment) Fab forming the arm and a constant heavy domain; and 1(crystallizable fragment) Fc forming the "base," made up of the remaining portions of both heavy chains. Antibodies are categorized into 5 distinct iso types – immunoglobulin G, immunoglobulin A, immunoglobulin M, immunoglobulin E, and immunoglobulin D – each characterized by unique structural and functional properties.
(7). Monoclonal antibodies (mAbs) are synthetic molecules engineered to mimic natural antibodies, enhancing or restoring the resistant system's ability to combat cancerous cells. They achieve this by official to specific antigens on the surface of malignant cell.

Classification and Types of monoclonal antibodies

There are 4 classification of monoclonal antibodies:

- (Murine)
- (Chimeric)
- (Humanized)
- (Human)

There are three classifications of mAbs based on their administration or application: bispecific, ,conjugated and unconjugated or naked.

Unconjugated monoclonal antibodies

These often referred to as "naked" mAbs, are antibodies that operate independently without any additional components.

Conjugated mAbs

A monoclonal antibody that is linked with a radioactive or chemotherapy specialist molecule is named a conjugate monoclonal counter acting agent

Bispecific mAbs

This distinctive category of mAb combines two different mAbs, enabling it to bind to two separate antigens simultaneously.(8)

Cytokines

Cytokines are essential in regulating the development and functionality of various immune and non-immune cells. Their roles encompass immune regulation, the pathogenesis of diseases, and, more recently, the modulation and treatment of immune-mediated disorders.(9) Cytokines can be categorized into several groups, lymphokines, (interferons) IFNs, monokines, and (transforming growth factors)TGFs(10)

Cytokine Receptors: The structure consists of two polypeptide chains: a ligand-binding α subunit and a receptor beta subunit. The type of target cell that cytokine interact with is decided by the nearness of particular layer receptors .(11)

Enzymes

These complex biomolecules, also known as biocatalysts, facilitate specific chemical reactions in other substances without undergoing any permanent changes themselves. For example, alteplase (Activase, TPA) is used to dissolve blood clots; Pulmozyme is a recombinant deoxyribonuclease which breaks down Deoxyribonucleic present in lung

mucus emissions; and imiglucerase (Cerezyme) is a recombinant enzyme used to treat Gaucher's disease, which involves bone degeneration and broadening of the spleen & liver. (Factor IX)Alphanine SD, Benefix, Bebulin VH, Profilnine SD, Proplex T, a member of the peptidase family S1, is a serine protease essential for blood coagulation. A deficiency in this enzyme leads to hemophilia B.. (12)

Vaccines

The majority of vaccines currently available utilize either inactivated (killed) or live attenuated (weakened) technologies. Inactivated vaccines are completely safe and non-infectious.(13)Additionally, there are DNA and RNA vaccines. These vaccines have become increasingly favored because of their economical nature, straightforward design and manufacturing processes, appealing biosafety characteristics, and, particularly for DNA vaccines, their stability..(14) . Vaccine development is a challenging, intricate, and expensive endeavor that involves clinical development, process development, and assay development. The associated risks are significant, as the majority of vaccine candidates do not succeed in preclinical or early clinical stages, with fewer than 1 in 15 candidates progressing to Phase II ultimately receiving licensure. Vaccine development necessitates robust project management frameworks and controls, along with the essential expertise of scientists and engineers.(15)

Clotting factors

Coagulation factors are a group of proteins responsible for controlling the conversion of fibrinogen, a soluble plasma protein, into fibrin, an insoluble polymer that shapes a gel-like organise, cell trapping and facilitating blood clotting..(16)

Antiense drugs

Antisense technology serves as a valuable addition to small molecule and protein-based drug discovery platforms by focusing on RNA as its target instead of proteins. This approach allows for the development of antisense drugs that can effectively bind to challenging protein-coding RNAs, including scaffold proteins and transcription factors, as well as noncoding RNAs and RNAs that pose direct toxicity to cells.(17)

Peptide therapeutics

The majority of peptide medications are delivered via the parenteral route, with around 75% administered as injections. The primary therapeutic applications of peptide drugs are found in the fields of metabolic disorders and oncology.(18)

Technological advances in biopharmaceutical

Formulation

3d printing

3D printing technology comprises four essential components: the design and development of digital models, digital slicing, conversion to G-code files, and the manufacturing of 3D printers. This technology offers significant competitive advantages over traditional manufacturing methods, particularly within the plan of complex structures and the generation of personalized medicate conveyance frameworks.

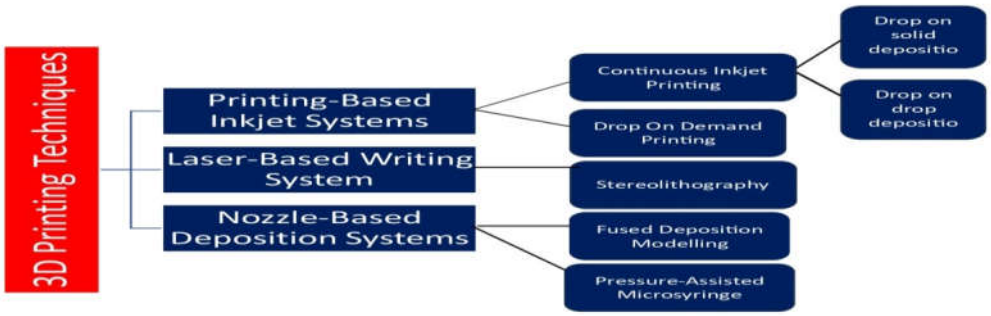

Figure 1 Classification of different 3 d printing technique

3D printing technologies

- Stereolithography (SLA)
- (Extrusion molding printing technology)EMP
  FDM technology
  (Semisolid extrusion molding technology)SSE
- (Selective laser sintering) SLS
- (Drop on powder printing)DOP
- (Electro hydrodynamic 3D printing)EHD(19)

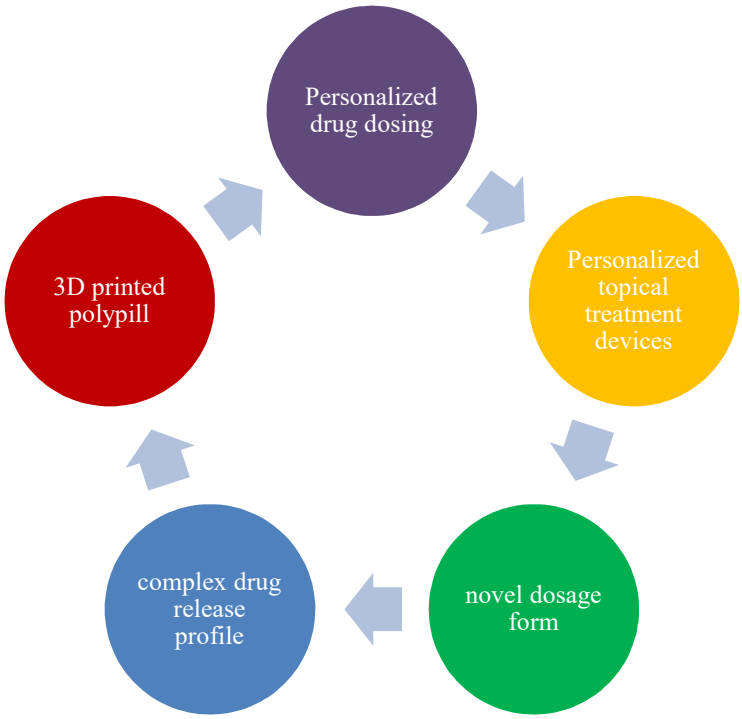

Figure 2 applications of 3 D printing technologies in drug delivery

Recent progress of 3d printing technologies in drug delivery application

- Personalized Drug Dosing
- Novel Dose Form and Drug Delivery Device
- Personalized Topical Treatment Device
- Complex Drug Release Profile
- 3D Printed Polypill(20)

Nanotechnology

Nanotechnology entails the engineering, fabrication, and manipulation of systems that merge chemical, physical, and biological entities at the atomic, molecular, or submicron scale. This field also emphasizes the assembly of these nanostructures into more elaborate systems..(21)

- Nanocarriers

  Polymeric nanocarriers.

Lipid nanocarriers.

- Self-dispersing ionic liquids-based nanostructures
- Microneedle-based devices.
- Cells-based therapies(22)

Challenges in biopharmaceutical formulation development

Stability

Stability liabilities include

a) Chemical instability, such as

1. Fragmentation/hydrolysis
2. Oxidation
3. Disulfide shuffling
4. Deamidation and succinimide formation

b) Physical instability, such as

1. Aggregation
2. Adsorption
3. Precipitation
4. Denaturation

Container closure system (ccs)

A conventional Container Closure System (CCS) comprises a glass vial, elastomeric plug, and Al seal, either alternatively, a prefilled syringe consisting of a glass cartridge, elastomeric plunger, and optional cannula or luer lock, accompanied by a rigid needle guard and plunger rod. The selection of the CCS is pivotal in the formulation of medicinal products..(23)

Innovations in formulation technique

Polymer–lipid pharmaceutical nanocarriers

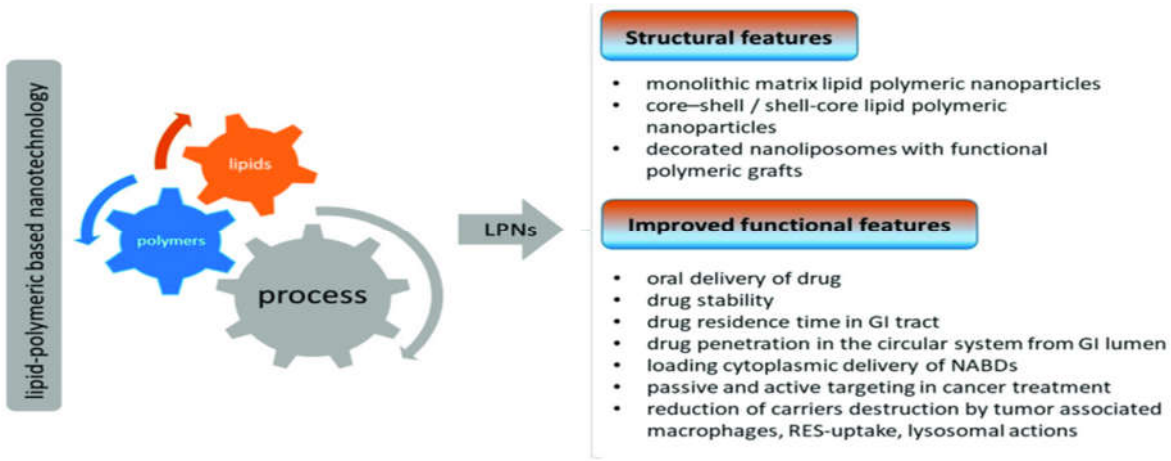

Figure 3 Schematic representation of potential improvements and structures of functional features of lipid–polymeric nanoparticles for pharmaceutical purposes.

Nanoparticle (NP) technology serves as an innovative sedate conveyance framework that optimizes the transport of dynamic compounds, thereby increasing their therapeutic efficacy while reducing adverse side effects, ultimately enhancing the treatment of various diseases.

Polymeric nanoparticles (PNs) act as biocompatible and biodegradable carriers, fabricated from diverse biomaterials, including naturally derived polymers such as (chitosan, hyaluronic acid, starch, dextran, alginate, albumin, and heparin).Additionally, their stimuli-responsive characteristics—responsive to factors such as temperature, power of hydrogen, redox conditions, and ionic strength facilitate exact control over the intracellular discharge of dynamic compounds.. Conversely, lipid nanoparticles are recognized as secure and viable carriers, inferred from either normal or engineered lipids. Commonly utilized lipids include fatty acids , glycerides , steroids, and various phospholipids .(24)

Lyophilization

This approach entails the dissolution of the drug substance in an organic solvent to achieve complete solubilization, followed by a careful filtration process to ensure sterility. In the course of lyophilization, the organic solvent will evaporate, resulting in a consistent lyophilized cake or powder, which can subsequently be reconstituted with a solvent to create a uniform suspension.

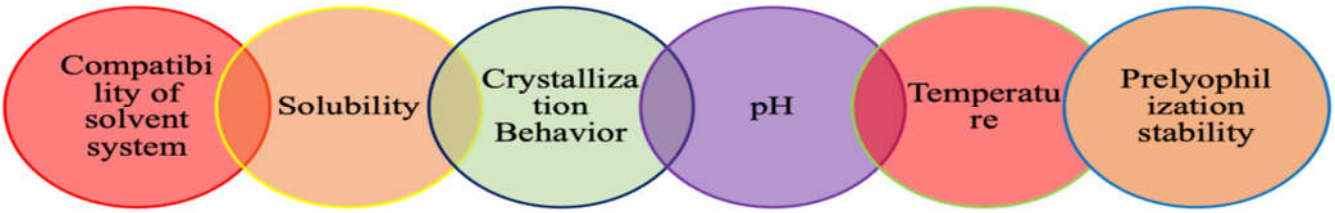

Figure 4 factors affecting drug product lyophilization

The lyophilization process is extensively employed in the production of pharmaceutical products under conditions of reduced temperature and pressure, ensuring their stability in a dried form for an extended duration. This technique is among the most prevalent methods for the manufacture of solid biopharmaceuticals, encompassing thermolabile substances, phospholipids, biologics, and vaccines, among others, to attain the desired shelf-life during storage and transportation.(25)

Microencapsulation

Microencapsulation refers to the technique of enclosing a substance within tiny capsules. This process allows for the coating of solid, liquid, and gaseous materials by creating a continuous film made of polymeric substances.(26)Microencapsulation is an rising innovation that protects sensitive food components and functional ingredients from antagonistic handling conditions by encapsulating them within a polymeric or non-polymeric matrix, enabling targeted and controlled release under predetermined conditions.(27)

Case study

Edible vaccines case study

The edible vaccine involves the integration of antigenic substances into the consumable portion of a plant, which, when taken orally, elicits an immune response. (28). The concept of edible vaccines was pioneered within the 1990s by Charles Arntzen, an American scholar . During a visit to India, Arntzen envisioned using fruits as a vehicle for immunization, leveraging their widespread availability in developing countries and the fact that they can be

consumed raw. Upon returning to the United States, he initiated research on tobacco plants as a means to test and approve his hypothesis. Arntzen's group effectively engineered tobacco plants to express the gene encoding the (hepatitis B virus surface antigen) HBsAg, resulting in the integration of this protein within the plant tissue. The recombinant hepatitis B virus surface antigen was extracted from transgenic plants using immunoaffinity chromatography and characterized via e microscopy, illustrating the feasibility of producing vaccine antigens in plant-based systems. Subsequent preclinical and clinical trials have yielded promising results, providing evidence for verbal immunization against the Norwalk infection and hepatitis B. Since 1995, researchers have harnessed various strains of Solanum tuberosum to develop consumable antibodies targeting hepatitis B, Norwalk infections, and E. coli-induced enteritis. (29)

Expression systems used for biopharmaceuticals production

A) Bacteria
B) Yeasts
C) Filamentous fungi
D) Insect cells
E)Mammalian cells
F)Transgenic plants
G)Transgenic animals(30)

Future trends and development

Trends in biopharmaceutical manufacturing

The rapid growth of biologics necessitates a deeper knowledge and optimization of biopharmaceutical production processes. This trend has sparked increased interest in leveraging (process analytical technology)PAT, which the Food and Drug administration defines as "a framework for planning, analyzing, and controlling fabricating through real-time estimations of basic quality and execution qualities of crude materials, in-process materials, and forms, with the extreme objective of guaranteeing the quality of the final product" A notable trend within the biopharmaceutical manufacturing sector is the move from bunch preparing to ceaseless operation. This transition aligns with the recent movement observed in the production of chemically derived pharmaceuticals, commonly alluded to as "small-molecule drugs," which is motivated by the desire to lower manufacturing costs while enhancing flexibility and quality. Additionally, there is significant interest in the creation of innovative designs for downstream processes, particularly in the area of protein separations. If these advancements prove successful, they could represent a significant transformation in biopharmaceutical manufacturing practices..(31)

2d & 3d inkjet printing of biopharmaceutical

The application of 3 D and 2 D printing technologies has been explored across various fields, from early-stage discovery to the production of pharmaceuticals. Key printing techniques employed in these applications include drop-on-demand and extrusion based methods.

(Drop-on-demand)DoD inkjet printers generate a single ink droplet only when necessary, triggered by a specific signal. Typically, these printers utilize either piezoelectric or thermally activated printheads, both of which supply energy to the fluid near the nozzle, facilitating the creation and ejection of a droplet onto a surface. Piezoelectric printheads feature various actuation modes, with three primary techniques employed in extrusion-based printing: pneumatic, mechanical, and solenoid. Inkjet printing or electrospray methods are mainly applied for the deposition of biopharmaceuticals in two-dimensional layers, where functional materials are placed onto a substrate on the x & y axes. In contrast, 3 D printing is utilized to create layer structures with considerable depth..(32)

Future prospects for biopharmaceuticals

In recent years, the biopharmaceutical sector has experienced a more rapid expansion compared to the overall pharmaceutical market. Analysts project that this trend will persist. The consistent rise in biopharmaceutical sales, both observed and expected, can be attributed to several factors, including the aging population, which has led to a higher prevalence of chronic illnesses, as well as an raise in the quantity of individuals suffering from diabetes and cancer, alongside a rise in autoimmune disease casesThe expansion rate of the biopharmaceuticals sector is likely to be greatly affected by advancements in molecular biology techniques and their automation, enhanced understanding of expression systems, and improved insights into the operational processes and technological elements associated with scaling up recombinant protein production. The biopharmaceutical market holds significant potential due to groundbreaking innovations, including the emergence of immunotherapy, antibody-drug conjugates, and gene therapies. Based on the information regarding the products currently undergoing clinical trials, a consistent rise in the number of newly registered monoclonal antibodies (mAbs) and their prominent role in the biopharmaceutical market can be anticipated..(33)

Regulatory agencies

Regulations are implemented by both domestic and foreign regulatory agencies, including the

EMA,U.S. FD , and the World Health Organization. A significant regulatory framework within the pharmaceutical sector for Quality Management Systems is the (International Council for Harmonisation) ICH Q10 guideline, known as Pharmaceutical Quality System . The ICH Q10 guideline outlines a pharmaceutical Quality Management System (QMS) framework that is grounded in ISO quality principles, emphasizing continuous improvement, and serves to enhance Good Manufacturing Practice (GMP) standards.(34) The (Food and Drug Administration)FDA US is pivotal in ensuring patient safety and supporting the economy. The FDA enforces standards set forth by Congress concerning the efficacy and safety of prescription medications, thereby allowing healthcare professionals

and patients to trust that approved pharmaceuticals will provide positive outcomes and maintain a reasonable level of safety..(35). The framework for regulatory approval of biosimilar medicines at the European Union level was established in 2005, which allowed the European Medicines Agency (EMEA, now known as EMA) to grant approval for the first biosimilar, Omnitrope, in 2006..(36)

Quality

Quality control

Quality control encompasses the processes of sampling, establishing specifications, and conducting tests, along with the organization, documentation, and procedures for release. These measures guarantee that all necessary and relevant tests are conducted, and that ingredients are only approved for use and products for sale or distribution after their quality has been verified as satisfactory..(37)

In contemporary pharmaceutical companies, product quality is of paramount importance. With the global convergence of stakeholders aimed at aligning with and implementing the good manufacturing practices recommended by the Food and Drug Administration , maintaining high product standards has become a primary focus for all regulatory agencies. To reduce regulatory obstacles that hinder innovation, creativity, and development costs, the International Conference on Harmonization and the FDA have initiated the promotion of "Qbd" within the pharmaceutical sector..(38) (Quality by Design)QbD is formally defined as an integrated product development approach. It begins with predefined objectives, emphasizing a comprehensive understanding of the item, process, and process control. This methodology is rooted in robust scientific principles and quality risk management. Unlike traditional(Quality by Testing) QbT, which primarily assesses quality in the final product, QbD integrates quality into every stage of product and process development.(39)

A quality system necessity

Efficient management of deviations within the biopharmaceutical sector is essential for maintaining product quality, adhering to regulatory standards, and safeguarding patient safety..(40)

Conclusion

Biopharmaceuticals have revolutionized the prevention, diagnosis, and treatment of various diseases, offering enhanced selectivity and reduced toxicity compared to traditional chemical drugs. This review has explored the definition, classification, and applications of biopharmaceuticals, including monoclonal antibodies, cytokines, enzymes, vaccines, clotting factors, antisense drugs, and peptide therapeutics. Recent technological advancements, such as 3D printing, nanotechnology, lyophilization, and microencapsulation, have improved biopharmaceutical formulation and delivery. The biopharmaceutical industry is poised for sustained expansion, driven by demographic

shifts, escalating chronic disease prevalence, and pioneering advancements in immunotherapy, antibody-drug conjugates, and gene therapies. Regulatory authorities, including the FDA, EMA, and WHO, play a pivotal role in safeguarding product quality and safety through guidelines such as Quality by Design (QbD) and International Council for Harmonisation (ICH) Q10. As the biopharmaceutical landscape undergoes transformation, ongoing innovation and research will be instrumental in tackling existing challenges and realizing the therapeutic potential of these lifesaving treatments.

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